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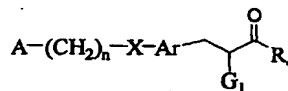
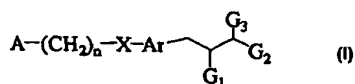
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: SUBSTITUTED ARALKYL DERIVATIVES



(57) Abstract: The present invention relates to novel substituted aralkyl derivatives of the general formula (I) & (IIIa), their deriva-
tives, their analogs, their tautomeric forms, their pharmaceutically acceptable salts, their pharmaceutically acceptable solvates, phar-
maceutical compositions containing them, use of these compounds in medicine and the intermediates involved in their preparation.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/91 C07D279/16 C07D413/04 C07D265/38 C07D209/86
 C07D215/14 C07D209/08 C07D213/30 C07D207/32 C07D235/06
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B. FIELDS SEARCHED

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IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, PAJ, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 91/19702 A (PFIZER) 26 December 1991 (1991-12-26) see general formula II, especially definitions of Z and Z'	9-22
Y	EP 0 930 299 A (JAPAN TOBACCO INC) 21 July 1999 (1999-07-21) cited in the application see definition of R' and examples 23,13.	9-22
E	WO 2004/031162 A (HOFFMANN LA ROCHE) 15 April 2004 (2004-04-15) see definitions of R3 and R4	1-22
P,Y	WO 02/092084 A (HOFFMANN LA ROCHE) 21 November 2002 (2002-11-21) cited in the application see definitions of R2,R3,R4,R6	1-22
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national Application No

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IPC 7 A61K31/47 A61K31/538 A61K31/4439 C07C43/03 A61P3/10

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Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>EGBERTSON M S ET AL: "NON-PEPTIDE FIBRINOGEN RECEPTOR ANTAGONISTS. 2. OPTIMIZATION OF A TYROSINE TEMPLATE AS A MIMIC FOR ARG-GLY-ASP" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 37, no. 16, 1994, pages 2537-2551, XP000574969 ISSN: 0022-2623 see examples 24a and 17</p>	1,2,4,7, 8,14,15
E	<p>WO 2004/004665 A (DEVASTHALE PRATIK ;SQUIBB BRISTOL MYERS CO (US); CHEN SEAN (US); Y) 15 January 2004 (2004-01-15) see RN 647006-18-6 and RN 647006-17-5</p>	1-4

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- * & * document member of the same patent family

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IN 03/00358

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 03/072102 A (CONNER SCOTT EUGENE ;MANTLO NATHAN BRYAN (US); LILLY CO ELI (US);) 4 September 2003 (2003-09-04) see definitions of Q,R3/R4 and A and example 38 ---	1-22
X	JP 51 149265 A (YOSHITOMI PHARMACEUT IND LTD) 22 December 1976 (1976-12-22) RN 62803-01-4 ---	1
X	EP 0 478 363 A (MERCK & CO INC) 1 April 1992 (1992-04-01) see compound 7-4, page 34 and experimental, page 35, lines 45-50 ---	1-4
Y	WO 96/38415 A (SUMITOMO METAL IND ;TAKENO HIDEKAZU (JP); IKEMOTO TOMOYUKI (JP); S) 5 December 1996 (1996-12-05) RN 185679-52-1 ---	1-22
X		1-4,7,8, 14,15
Y	WO 01/40170 A (ASTRAZENECA AB ;FAEGERHAG JONAS (SE); LI LANNA (SE); LINDSTEDT ALS) 7 June 2001 (2001-06-07) cited in the application especially definitions of A the whole document -----	1-22

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 17-21 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 1-5 (partly), 7, 8 (partly), 14-22 (partly)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/ IN 03 /00358

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5 (partly), 7, 8 (partly), 14-22 (partly)

Present claims 1-5, 7, 8, 14-22 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds of formula I wherein A is a heterocycle, Ar is a 1,4-phenylene and X is O, and all of the examples.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/IN 03/00358

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9119702	A	26-12-1991	US 5089514 A	18-02-1992
			AT 149156 T	15-03-1997
			AU 646052 B2	03-02-1994
			AU 7995691 A	07-01-1992
			CA 2084898 A1	15-12-1991
			DE 69124798 D1	03-04-1997
			DE 69124798 T2	12-06-1997
			DK 533781 T3	07-07-1997
			EP 0533781 A1	31-03-1993
			ES 2098356 T3	01-05-1997
			FI 925640 A	11-12-1992
			GR 3022714 T3	30-06-1997
			HU 65603 A2	28-07-1994
			IE 912003 A1	18-12-1991
			IL 98447 A	31-12-1995
			JP 2581523 B2	12-02-1997
			JP 7149636 A	13-06-1995
			JP 7005513 B	25-01-1995
			JP 5507920 T	11-11-1993
			NO 924799 A	14-12-1992
			NZ 238528 A	27-07-1993
			PT 97950 A ,B	31-03-1992
			WO 9119702 A1	26-12-1991
			US 5438074 A	01-08-1995
			US 5306726 A	26-04-1994
			ZA 9104519 A	27-01-1993
EP 0930299	A	21-07-1999	JP 3215048 B2	02-10-2001
			JP 9323982 A	16-12-1997
			AU 740444 B2	01-11-2001
			AU 3866597 A	06-03-1998
			BG 103268 A	29-12-2000
			BR 9711627 A	24-08-1999
			CA 2263721 A1	26-02-1998
			EE 9900069 A	15-10-1999
			EP 0930299 A1	21-07-1999
			NO 990700 A	19-04-1999
			NZ 334738 A	26-01-2001
			PL 331861 A1	16-08-1999
			SK 21099 A3	16-05-2000
			US 6204277 B1	20-03-2001
			CN 1233241 A	27-10-1999
			CZ 9900536 A3	14-07-1999
			WO 9807699 A1	26-02-1998
WO 2004031162	A	15-04-2004	WO 2004031162 A1	15-04-2004
WO 02092084	A	21-11-2002	CA 2445145 A1	21-11-2002
			WO 02092084 A1	21-11-2002
			EP 1392295 A1	03-03-2004
			NO 20035086 A	14-11-2003
			US 2003055265 A1	20-03-2003
WO 2004004665	A	15-01-2004	WO 2004004665 A2	15-01-2004
			US 2004063700 A1	01-04-2004
WO 03072102	A	04-09-2003	WO 03072102 A1	04-09-2003

INTERNATIONAL SEARCH REPORT

national application no

PCT/IN 03/00358

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
JP 51149265	A	22-12-1976	NONE	
EP 0478363	A	01-04-1992	AT 150454 T	15-04-1997
			AU 655436 B2	22-12-1994
			AU 8478291 A	02-04-1992
			CA 2052073 A1	28-03-1992
			CY 2048 A	30-04-1998
			DE 69125235 D1	24-04-1997
			DE 69125235 T2	07-08-1997
			DK 478363 T3	12-05-1997
			EP 0478363 A2	01-04-1992
			EP 0743302 A2	20-11-1996
			ES 2100214 T3	16-06-1997
			ES 2133892 T3	16-09-1999
			FI 914534 A	28-03-1992
			FI 20011201 A	06-06-2001
			GR 3023226 T3	30-07-1997
			GR 3031473 T3	31-01-2000
			HK 1000509 A1	03-04-1998
			HR 930779 A1	28-02-1997
			IE 913383 A1	08-04-1992
			IL 99540 A	31-07-1995
			JP 2812431 B2	22-10-1998
			JP 9132558 A	20-05-1997
			JP 4288051 A	13-10-1992
			JP 7094425 B	11-10-1995
			KR 216939 B1	01-09-1999
			LU 90505 A9	20-03-2000
			LV 5746 A4	20-10-1996
			LV 12089 A	20-07-1998
			LV 12089 B	20-11-1998
			NO 913784 A ,B,	30-03-1992
			NZ 239846 A	25-11-1994
			PT 99098 A ,B	31-08-1992
			SG 63636 A1	30-03-1999
			SI 9210306 A ,B	31-08-1995
			WO 9319046 A1	30-09-1993
			US 5880136 A	09-03-1999
			US 6040317 A	21-03-2000
			US 5658929 A	19-08-1997
			US 5292756 A	08-03-1994
			US 5814643 A	29-09-1998
			ZA 9107661 A	27-05-1992
			CN 1069971 A ,B	17-03-1993
WO 9638415	A	05-12-1996	JP 8325263 A	10-12-1996
			AU 5779196 A	18-12-1996
			WO 9638415 A1	05-12-1996
WO 0140170	A	07-06-2001	AU 766547 B2	16-10-2003
			AU 2240101 A	12-06-2001
			BR 0016133 A	20-08-2002
			CA 2392035 A1	07-06-2001
			CN 1433401 T	30-07-2003
			EP 1237857 A1	11-09-2002
			JP 2003515581 T	07-05-2003
			NO 20022603 A	10-07-2002
			NZ 518922 A	28-11-2003

INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0140170	A	WO 0140170 A1 US 2003018207 A1 ZA 200203703 A	07-06-2001 23-01-2003 11-08-2003
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